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Research Article

Thyroid function determinants in cord blood of Nigerian neonates

Rebecca M. Gali[1], Iya E. Bassey[2]*, Alphonsus E. Udoh[2], Chinyere A. O. Usoro[2], Calvin M. Chama[3], Uwem O. Akpan[2]

[1]Department of Medical Laboratory Science, College of Medical Sciences, University of Maiduguri, Borno State, Nigeria
[2]Department of Medical Laboratory Science, Faculty of Allied Medical Sciences, College of Medical Sciences, University of Calabar, Cross River State, Nigeria
[3]Department of Obstetrics and Gynaecology, College of Medical Sciences, University of Maiduguri, Borno State, Nigeria

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***Correspondence:**
Dr. Iya E. Bassey,
E-mail: iyantui@yahoo.com

ABSTRACT

Background: Congenital hypothyroidism is one of the most prevalent endocrine disorders in the newborn; early diagnosis and treatment have resulted in normal growth and development in nearly all cases. Data on congenital hypothyroidism in Nigeria is limited, hence, this study aims at establishing the baseline values and prevalence of congenital hypothyroidism as a prelude to a screening centre in our locality.
Methods: Cord blood samples were consecutively obtained from two hundred and eighty nine neonates born in the Delivery ward of the University of Maiduguri Teaching Hospital (UMTH). 152 (52.8%) of the neonates were males and 137 (47.2%) were females. Nineteen were preterm and 270 were full term. Triiodothyronine (T3), Thyroxine (T4) and Thyroid-stimulating hormone (TSH) were analyzed using ELISA kits. Data was analyzed using student "t" test and Pearson correlation coefficient. The difference was considered statistically significant at $p < 0.05$.
Results: The mean T3, T4 and TSH, in preterm compared with full term neonates were similar ($p>0.05$). Triiodothyronine (T3) was undetectable in 75.8% of the neonates and very low in 24.2%. Twelve (4.2%) of the neonates had TSH levels >40µIU/ml with a mean TSH of 61.7±14.7 µIU/ml and a mean T4 of 7.7±3.7µg/dl.
Conclusions: About 4.2% of neonates are at risk of congenital hypothyroidism with High TSH and low T4 values, T3 values are undetectable or very low in late prenatal life.

Keywords: Cord serum, Thyroid hormones, Neonates

INTRODUCTION

Thyroid hormones are required for normal development of the human fetal brain and for the maturation of other organs and functions.[1,2] The metabolic rate of every cell, except the red blood cell, in the body is regulated by thyroid hormones.[3] Congenital hypothyroidism is the most prevalent endocrine disorder in the newborn and affects 1 in 3,000–4,000 newborns.[4] Neonatal hypothyroidism may be due to inborn iodine deficiency or as a result of maternal hypothyroidism.[5,6] Despite the critical importance of thyroid hormone on multiple organ systems, especially the brain, most infants with congenital hypothyroidism appear normal at birth.[7] Deficiencies may be detected during screening, with early diagnosis and treatment normal development is possible in nearly all cases.[4] Cord blood provides important indices of problems affecting the fetus and the newborn as well as future adult problems.[8] The venous cord blood (VCB) values of many biochemical parameters given in classical sources are based on studies made many years ago and in the western world.[9,10] Moreover, some authors have stated that their own data are not in agreement with

classical values.[11] This suggests possible demographic differences in the values of the parameters. Therefore, there is a need to obtain reliable data that can be of use in the relevant environment. Data on congenital hypothyroidism in Nigeria is limited and scarce, hence, this study aims at establishing the baseline values and prevalence of congenital hypothyroidism in Maiduguri, Borno state.

METHODS

Study design and subject selection

This cross sectional study was carried out at the Maternity ward of University of Maiduguri Teaching Hospital (UMTH), Maiduguri, Borno State, Nigeria. Ethical clearance was obtained from the Ethical Committee of the UMTH. Informed consent of the mothers was sought during the antenatal clinics before recruitment into the study. The mothers who consented and were apparently healthy during delivery were included in the research, whereas neonates whose mothers had known history of diabetes mellitus, hypertension, eclampsia, Graves' disease, goiter, and those on chronic medication for any reason were excluded from the study. The gestational ages of the neonates ranged from 32 to 42 weeks. In our study, preterm neonates were defined as neonates of gestational age 32-36 weeks and full term neonates as neonates of gestational age 37-42 weeks. The mothers were given a standard questionnaire to obtain socio-demographic details of the study population. Anthropometric indices of the neonates were also measured.

Sample collection

Medical doctors and trained nurses in the delivery ward collected the cord blood after the birth of the baby. The cord was double clamped and divided. The placental end of the cord was cleaned with dry gauze and the umbilical vein identified. Five-milliliter syringe and needle was used to aspirate 5ml of blood from the umbilical vein which was put into a properly labeled clean plain specimen bottles and allowed to clot. The blood was centrifuged after clotting and the serum separated and stored in the refrigerator at −20^{o}C for batch analysis.

Anthropometric indices

The neonates were weighed (in kilograms) with Bessinet neonatal weighing scale, made by SALTER England, Model 180 and their length (in metres) were taken using standard measuring tape. Body mass index (BMI) was computed as the ratio of weight (kilograms) to the square of height (meters).

T_3, T_4 and TSH assays

Enzyme Linked Immunosorbent Assay kits specific for T3, T4 and TSH obtained from DRG International, California, USA were used for the analyses. The serum total T3 and T4 assays were performed as described by Schall et al[12] and TSH as described by Uotila et al[13].

Statistical analysis

This was done using the PAWstatistic 18, a statistical package from SPSS Inc, California, USA. The results were expressed as Mean ± SD. The data was analyzed by Student's t-test and analysis of variance (ANOVA). Post-hoc analysis was done using Fischer's least significant difference (LSD). Pearson's correlation analysis was used to determine relationship between different variables. The level of significance was set at 95% confidence interval, where a two-sided p-value less than 0.05 ($p<0.05$) was considered as statistically significant.

RESULTS

One hundred and fifty two (52.8%) of the 289 neonates were males and one hundred and thirty seven (47.2%) were females. There were nineteen (6.6%) preterm neonates and two hundred and seventy (93.4%) full term neonates. Triiodothyronine (T_3) was not detectable in 75.8% of the neonates and found at very low levels in 24.2%. The mean values and ranges of anthropometric indices, gestational age, T_3, T_4 and TSH obtained for all neonates are shown in Table 1. A comparison of BMI and Cord blood T_3, T_4 and TSH in preterm and full-term neonates showed no significant differences ($p>0.05$) between both groups (Table 2). The mean BMI, T_3, T_4 and TSH, for both male and female neonates were also similar ($p>0.05$) (Table 3).

Table 1: Mean values and ranges of anthropometric indices, gestational age and thyroid hormone parameters for all neonates.

Parameters	N	Mean ± SD	Range
BMI (kg/m^2)	289	13.25± 2.28	8.8−17.7
Weight (kg)	289	3.12 ±0.55	2.0−4.2
Gestational age (wk)	289	38.32 ±1.58	35.2−41.4
T_3 (ng/ml)	289	0.13 ±0.28	0−0.7
T_4 (µg/dl)	289	10.74 ±7.71	0−25.9
TSH (µIU/ml)	289	12.74 ±12.52	0−37.3

Mean ± SD

Table 2: Mean vales of body mass index and cord blood T3, T4 and TSH in preterm and full-term neonates.

Parameters	Preterm (n=19)	Term (n=270)	p-value
T_3 (ng/ml)	0.17± 0.30	0.13± 0.28	0.46
T_4 (µg/dl)	11.04±4.71	10.71±7.88	0.58
TSH (µIU/ml)	11.11±6.47	12.86±12.84	0.16
BMI(kg/m^2)	12.24±2.41	13.65±2.25	0.32

Mean ± SD

Table 3: Mean values of body mass index, cord serum T_3, T_4, TSH in male and female neonates.

Parameters	Male (n=152)	Female (n=137)	p-value
T_3 (ng/ml)	0.14± 0.28	0.13± 0.28	0.44
T_4 (µg/dl)	10.68±8.22	10.80±7.12	0.76
TSH (µIU/ml)	13.08±12.99	12.36±12.02	0.23
BMI(kg/m^2)	13.92±2.57	13.16±1.84	0.58

Mean ± SD

The neonates were classified into 3 groups based on the updated American Academy of Pediatrics (AAP) Guidelines on Newborn Screening and Therapy for Congenital Hypothyroidism 14; those with TSH values less than 20 µIU/ml were classified as normal; those with TSH values 20-40 µIU/ml were above upper reference value but within statistical range for this study population 0-37 µIU/ml (table 1) and TSH values above 40 µIU/ml were classified as high. 88.2% had normal TSH values, 7.6% had moderately high TSH values, while 4.2% had high values. The mean T_4 of the third group was lower though not significantly (p>0.05) so than the mean T_4 of each of the other two groups (Table 4).

Table 4: Comparison of T_4 values in neonates with normal, moderately elevated and elevated TSH values.

Subjects	n	TSH (µIU/ml)	T4 (ug/dl)
Normal (< 20µIU/ml)	255 (88.2%)	9.33±5.81	10.85±7.63
Moderately high (20 - 40µIU/ml)	22 (7.6%)	27.01±5.98	11.36±9.97
High (above 40µIU/ml)	12 (4.2%)	61.71±14.71	7.72±3.68

Mean ± SD

A significant negative correlation (r = - 0.131; p=0.026) was observed between T4 and TSH (Figure 1).

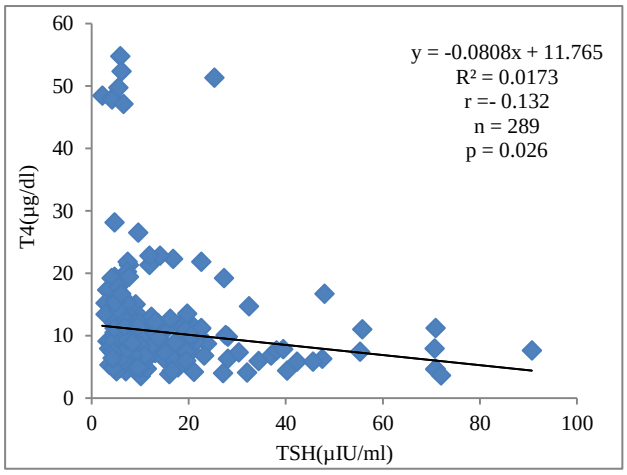

Figure 1: A Scatter plot correlation between T4 and TSH in neonates.

DISCUSSION

Cord blood provides data on problems that concern neonates including factors that may serve as indicator for future problems. This is the first prospective study to examine the levels of thyroid hormones in neonates using cord blood in our environment. This suggests that the gland produces almost exclusively thyroxine (T_4) and that T_3 either has a minimal functional role at this stage or it is used up as quickly as it is made. In a study by Santini et al, in 1999, he observed that type III-MD is important in regulating the metabolism of iodothyronines originated in the fetus. The major role of this enzyme consists of maintaining serum T_3 at a low level during intrauterine life, by supporting a high metabolic clearance rate of this hormone. It achieves this by T_3-to-T_2 conversion, as well as catalyzing the monodeiodination of T_4 to rT_3. They suggested that this mechanism has a particular relevance in late gestation, because it prevents a rise in neonatal serum T_3 levels, while allowing a maturation of the peripheral machinery (type I-MD) responsible for the production of T_3.[15] Similar observations were made by Kester et al in 2004.[16] The physiological significance of low circulating T_3 concentrations throughout gestation is not known, however, it has been suggested that its function may be to avoid tissue thermogenesis and potentiate the anabolic state of the rapidly growing fetus.[17] Results from our study showed that there were no significant differences in cord serum thyroid hormones between the preterm and full term babies. This suggests that the same reference range for T_3, T_4 and TSH used for full term babies can also be used for preterm babies.

Cord blood TSH and T_4 are major tools in the diagnosis of congenital hypothyroidism. The TSH is considered more sensitive than T_4, but both are often used simultaneously. The statistical range of TSH in this neonate population was 0 to 37.3 µIU/ml. Earlier studies had recommended various reference values for TSH beyond which the neonate should be considered at risk of congenital hypothyroidism. These include TSH>20 µIU/ml,[18] TSH>30 µIU/ml,[19] TSH>40 µIU/ml[14] and TSH>50 µIU/ml.[20] There is even a suggestion that the reference value should be reset to >90 µIU/ml.[21] The impression one gets from this wide-ranging differences is that a universal reference value for TSH in the diagnosis of congenital hypothyroidism may be misleading. Individual testing laboratories should determine the appropriate reference values for their environments. The upper limit of the range of TSH values for our neonate population was 37.3µIU/ml. These findings appear to justify, at least in our own case, the suggested reference value of 40 µIU/ml for TSH. Twelve of the neonates (4.2%) had TSH values above 40 µIU/ml. These neonates are at risk of congenital hypothyroidism and need to be followed up. The percentage at risk of developing congenital hypothyroidism in this study is large when compared to the worldwide incidence of 1 in 4000.[22] In two separate research in India using cord blood one

reported 1 in 248[23] and the other 1 in 600 neonates,[18] while in Iran 1 in 914 and 1 in 1700 was reported.[24,25]

Correlation graph of T_4 against TSH as shown in figure 1 revealed a significant inverse relationship. This was expected, since a high TSH often is induced by hypo activity of the thyroid gland except in secondary hyperthyroidism where high TSH is responsible for excess thyroid hormone synthesis and release.[26] In this study, cord blood T_4 range between 0 and 26 µg/dl. This range is much wider than is seen in adults. Some of the T_4 is believed to be of maternal origin.[15] Tetraiodothyronine is essential for normal early fetal neurogenesis and is highly regulated to maintain relatively low concentrations essential for protecting the fetus and reaching key neurological sites such as the cerebral cortex at specific developmental stages.[27] Neonatal screening programmes for detection of congenital hypothyroidism have been in practice in the developed countries for the last four decades[28] as well as in some developing countries.[29,30] However, in many countries in Sub-Saharan Africa, including Nigeria, such screening programmes are still non-existent. In most screening programs blood samples were collected at 5-6 days of life. However, some studies have used cord blood for this purpose in Asian countries.[31,24] There were no significant differences between the values of T_3, T_4 and TSH cord blood and blood collected 72 hours after birth.[32] In some countries such as Nigeria, it is very difficult to call back babies once they are discharged from hospitals or maternity homes and most of the babies are discharged within 48 hours of delivery. There is also no effective social system where babies could be reached at home, thus cord blood remains a very practical alternative for screening purposes.

CONCLUSION

This study showed that 4.2% of the neonates are at risk of developing congenital hypothyroidism. Screening of neonates for congenital hypothyroidism is therefore crucial for early diagnosis and management. We recommend screening on a wider scale to determine actual prevalence of neonates at risk of congenital hypothyroidism in Nigeria.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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